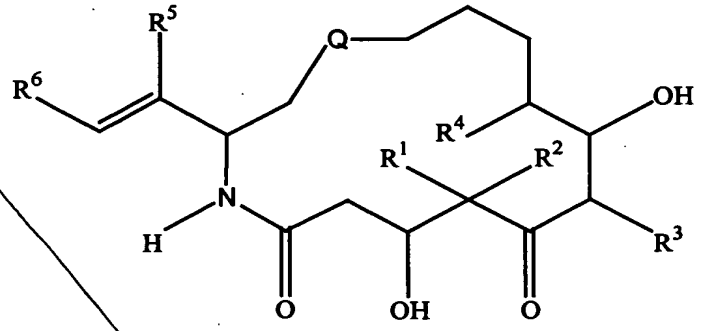
The Claims

What is claimed is:

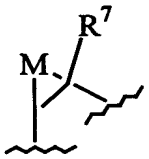
1. A process for formulating, for parenteral administration, an epothilone analog represented by formula I:



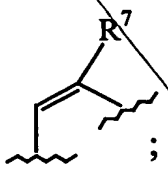
I

wherein:

Q is selected from the group consisting of:



and



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C{=}O$, $R^{12}OC{=}O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C{=}O$, and $R^{15}OC{=}O$;

and any salts, solvates, or hydrates thereof, comprising the following steps carried out under protection from light:

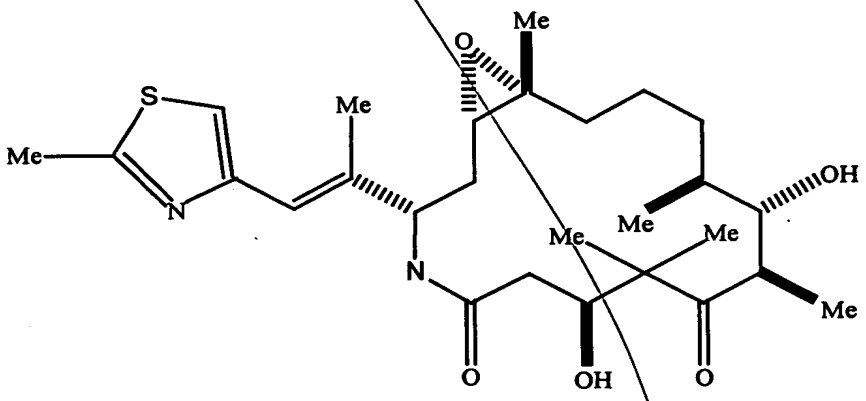
a) dissolving said epothilone analog in a mixture of at least about 50% by volume tertiary-butanol in water to form a solution;

b) performing primary drying of said solution at a temperature of from about -10EC to about -40EC under high vacuum of from about 50 millitorr to about 300 millitorr for from about 24 hours to about 96 hours to form a lyophilized product;

c) performing secondary drying of the resultant lyophilized product at a temperature of from about 10 EC to about 30EC under high vacuum of from about 50 millitorr to about 300 millitorr for from 24 hours to about 96 hours; and

d) packaging said lyophilized product in a first vial in combination with a second vial containing a sufficient quantity of an equal mixture by volume of a suitable nonionic surfactant and anhydrous ethanol to effect solution thereof.

2. The process of claim 1 wherein said epothilone analog is represented by formula II:



II

3. The process of claim 1 wherein in step a) said analog is first wetted with a mixture of at least about 60% tertiary-butanol in water, and then sufficient water, or a mixture of tertiary-butanol and water, is added thereto so that the resulting solution contains from about 2 mg/mL to about 30 mg/mL of said analog in a mixture of from about 50% to about 80% by volume tertiary-butanol in water.

4. The process of claim 2 wherein in step a) said analog is first wetted with a mixture of at least about 60% tertiary-butanol in water, and then sufficient water, or a mixture of tertiary-butanol and water, is added thereto so that the resulting solution contains from about 2 mg/mL to about 30 mg/mL of said analog in a mixture of from about 50% to about 80% by volume tertiary-butanol in water.

5. The process of claim 3 wherein in step a) said analog is initially wetted with a mixture of from about 60% to about 95% by volume tertiary-butanol in water.

6. The process of claim 4 wherein in step a) said analog is initially wetted with a mixture of from about 60% to about 95% by volume tertiary-butanol in water.

7. The process of claim 1 wherein said primary drying in step b) is carried out at a temperature of about -25°C and a pressure of about 200 millitorr for about 48 hours.

8. The process of claim 2 wherein said primary drying in step b) is carried out at a temperature of about -25°C and a pressure of about 200 millitorr for about 48 hours.

9. The process of claim 1 wherein said secondary drying in step c) is carried out at a temperature of about 25°C and a pressure of about 150 millitorr for about 48 hours.

10. The process of claim 2 wherein said secondary drying in step c) is carried out at a temperature of about 25°C and a pressure of about 150 millitorr for about 48 hours.

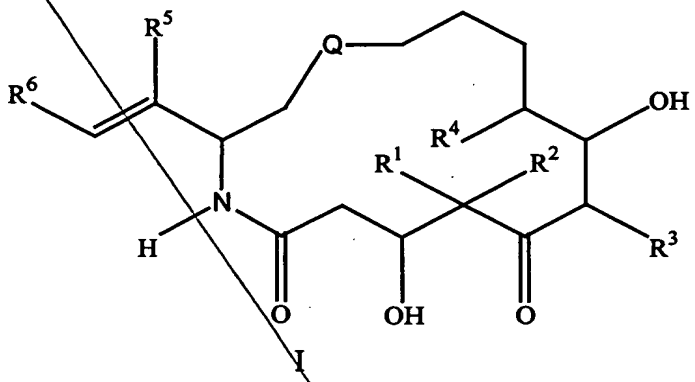
11. The process of claim 1 wherein said surfactant is polyethoxylated castor oil.

12. The process of claim 2 wherein said surfactant is polyethoxylated castor oil.

13. The process of claim 11 wherein said second vial contains an amount of said mixture sufficient to form a solution of from about 2 mg/mL to about 4 mg/mL of said analog therein.

14. The process of claim 12 wherein said second vial contains an amount of said mixture sufficient to form a solution of from about 2 mg/mL to about 4 mg/mL of said analog therein.

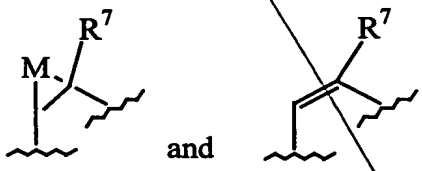
15. A pharmaceutical preparation comprising, in separate vials, a lyophilized epothilone analog and a quantity of a solvent therefor such that when the contents of said vials are combined, the resulting solution contains from about 2 mg/mL to about 4 mg/mL of said analog, said solvent comprising a mixture of about equal parts by volume of dehydrated ethanol and a suitable nonionic surfactant, said analog being represented by formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form cycloalkyl;

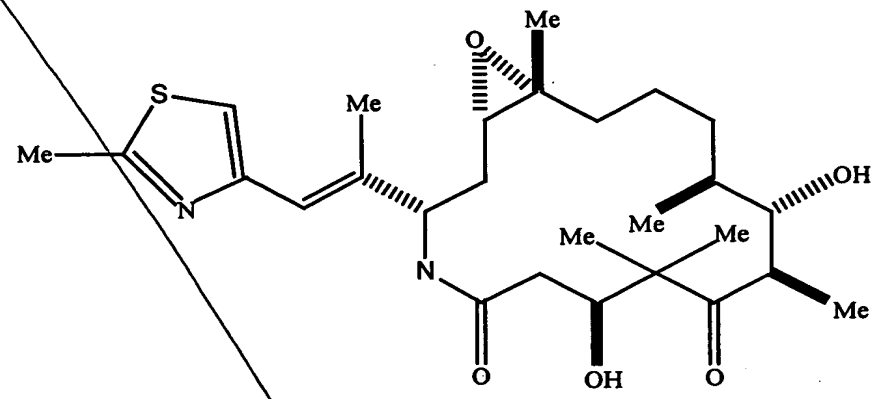
R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C{=}O$, $R^{12}OC{=}O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof.

16. The pharmaceutical preparation of claim 15 wherein said epothilone analog is represented by formula II:



II

17. The pharmaceutical preparation of claim 15 wherein said nonionic surfactant is polyethoxylated castor oil.

18. A process for forming a pharmaceutical composition for parenteral administration comprising mixing the contents of the vials of the pharmaceutical preparation of claim 15 to effect solution of said lyophilized epothilone analog and diluting the resultant solution with a quantity of a suitable parenteral diluent such that the concentration of said analog therein will be from about 0.1 mg/mL to about 0.9 mg/mL.

19. A process for forming a pharmaceutical composition for parenteral administration comprising mixing the contents of the vials of the pharmaceutical preparation of claim 16 to effect solution of said lyophilized epothilone analog and diluting the resultant solution with a quantity of a suitable parenteral diluent such that the concentration of said analog therein will be from about 0.1 mg/mL to about 0.9 mg/mL.

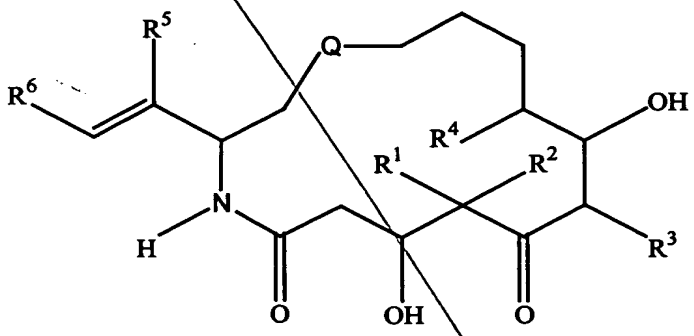
20. A process for forming a pharmaceutical composition for parenteral administration comprising mixing the contents of the vials of the pharmaceutical preparation of claim 17 to effect solution of said lyophilized epothilone analog and diluting the resultant solution with a quantity of a suitable parenteral diluent such that the concentration of said analog therein will be from about 0.1 mg/mL to about 0.9 mg/mL.

21. The process of claim 18 wherein said diluent is Lactated Ringer's Injection.

22. The process of claim 19 wherein said diluent is Lactated Ringer's Injection.

23. The process of claim 20 wherein said diluent is Lactated Ringer's Injection.

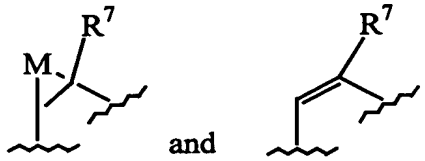
24. A method for treating a patient in need of treatment with an epothilone analog represented formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

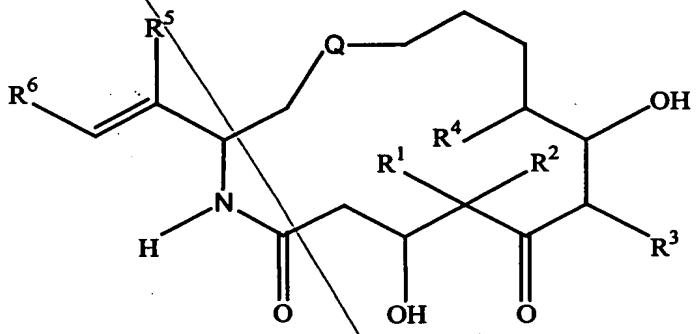
R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof, comprising administering to said patient, by intravenous injection, an effective amount of a pharmaceutical composition of claim 18.

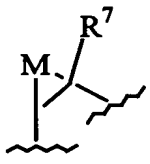
25. A method for treating a patient in need of treatment with an epothilone analog represented formula I:



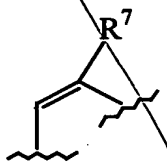
I

wherein:

Q is selected from the group consisting of



and



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

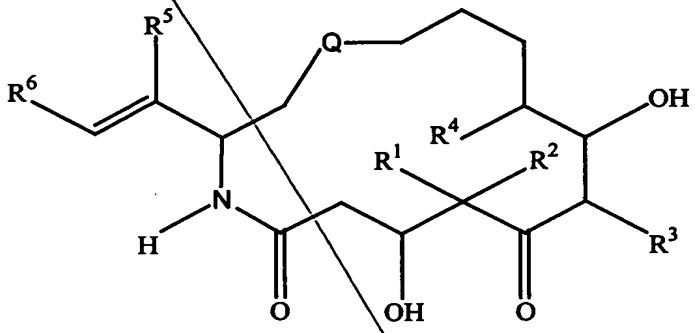
R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof, comprising administering to said patient, by intravenous injection, an effective amount of a pharmaceutical composition of claim 19.

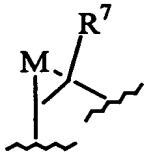
26. A method for treating a patient in need of treatment with an epothilone analog represented formula I:



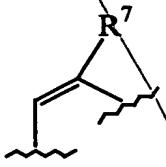
I

wherein:

Q is selected from the group consisting of



and



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

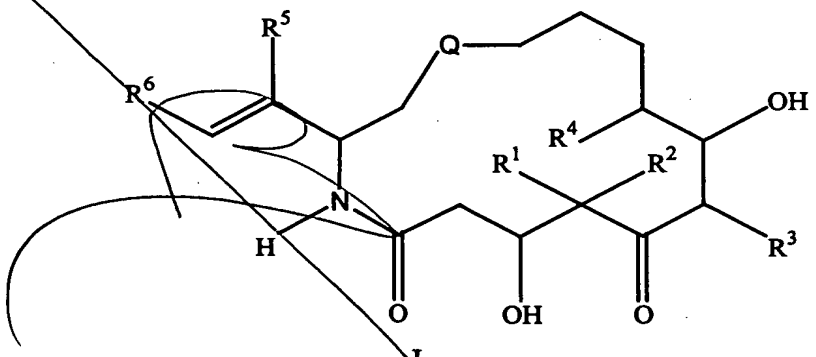
and any salts, solvates, or hydrates thereof, comprising administering to said patient, by intravenous injection, an effective amount of a pharmaceutical composition of claim 20.

27. The method of claim 24 wherein said diluent is Lactated Ringer's Injection.

28. The method of claim 25 wherein said diluent is Lactated Ringer's Injection.

29. The method of claim 26 wherein said diluent is Lactated Ringer's Injection.

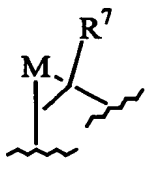
30. A method of treating cancer in a patient comprising intravenously and orally administering to said patient a therapeutically effective amount of a compound represented by formula I:



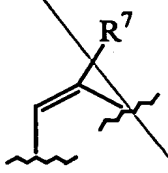
I

wherein:

Q is selected from the group consisting of



and



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO^2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof.

31. The method of claim 30, wherein the compound of formula I is administered orally in a dose of about 0.05 mg/kg to 200 mg/kg.

32. The method of claim 31, wherein the compound of formula I is administered intravenously at a dose of about 1 mg/m^2 to 65 mg/m^2.

33. The method of claim 32, wherein the compound of formula I is administered intravenously at a dose of about 25 mg/m^2.

34. The method of claim 30, wherein the compound of formula I is administered either orally or intravenously on a weekly basis.

35. The method of claim 34, wherein a 3 week cycle of intravenous administration is used.

36. The method of claim 35, wherein the compound of formula I is administered orally before the 3 week cycle.

37. The method of claim 35, wherein the compound of formula I is administered orally after the 3 week cycle.

38. The method of claim 31, wherein the compound of formula I is administered as one or more 28 day cycles, wherein the compound of formula I is administered as an IV infusion on days 1, 7, and 14 and orally on day 21.

39. The method of claim 31, wherein the IV infusion is administered over a period of about 45 minutes to 90 minutes.

40. The method of claim 39, wherein the IV infusion is administered over a period of about 1 hour.

41. The method of claim 31, further comprising administering to said patient one or more additional therapeutic agents to prevent nausea, vomiting, hypersensitivity, or gastric irritation.

42. The method of claim 41, wherein the one or more additional therapeutic agents is an H_1 or H_2 antihistamine.

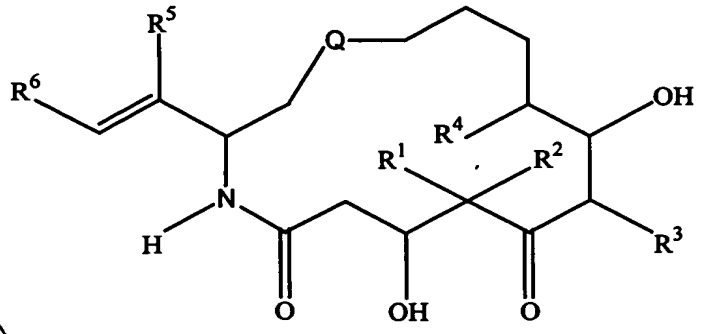
43. The method of claim 31, wherein the patient has not previously been treated for cancer.

44. The method of claim 31, wherein the patient has been previously treated for cancer.

45. The method of claim 31, wherein the cancer is refractory to radiation therapy.

46. The method of claim 31, wherein the cancer is refractory to anti-cancer chemotherapy.

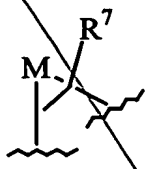
47. A pharmaceutical composition suitable for parenteral administration comprising a compound represented by formula I:



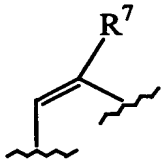
I

wherein:

Q is selected from the group consisting of



and



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C{=}O$, $R^{12}OC{=}O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C{=}O$, and $R^{15}OC{=}O$;

and any salts, solvates, or hydrates thereof;

dehydrated alcohol; and

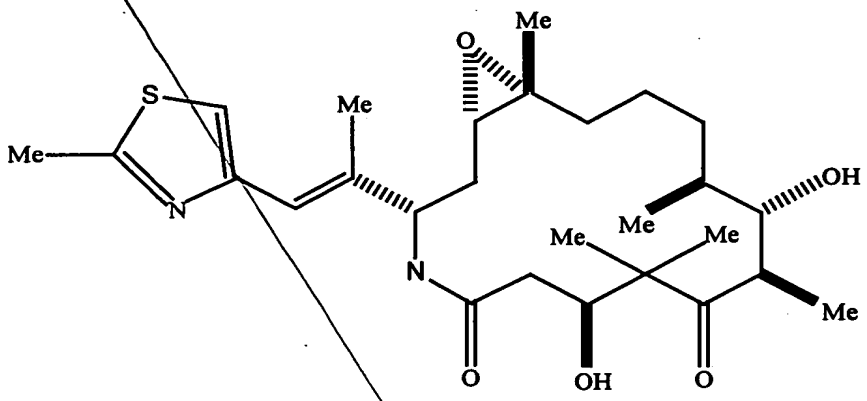
a non-ionic surfactant.

48. The composition of claim 47, wherein the surfactant is polyethoxylated castor oil.

49. The composition of claim 47, wherein the surfactant is Cremophor EL®.

50. The composition of claim 47, wherein the concentration of the compound of formula I is from about 2 mg/mL to 4 mg/mL.

51. The composition of claim 47, wherein the compound of formula I is



52. A method of treating cancer in a patient comprising intravenously administering to said patient a therapeutically effective amount of the pharmaceutical formulation of claim 47 diluted in a parenteral diluent.

53. The method of claim 52, wherein the parenteral diluent is 5% dextrose, lactated ringer's and dextrose injection, or sterile water for injection.

54. The method of claim 52, wherein the concentration of the compound of formula I in the parenteral diluent is about 0.1 mg/mL to 0.9 mg/ mL.

55. The method of claim 52, wherein the compound of formula I is administered in a dose of about 1 mg/m^2 to 65 mg/m^2.

56. The method of claim 55, wherein the compound of formula I is administered at a dose of about 25 mg/m^2.

57. The method of claim 52, wherein the pharmaceutical composition is administered as weekly as an IV infusion.

58. The method of claim 52, wherein the IV infusion is administered over a period of about 45 minutes to 90 minutes.

59. The method of claim 52, wherein the IV infusion is administered over a period of about 1 hour.

60. The method of claim 52, further comprising administering to said patient one or more additional agents to prevent nausea, vomiting, hypersensitivity, or gastric irritation.

61. The method of claim 60, wherein the one or more additional agents is an H_1 or H_2 antihistamine.

62. The method of claim 52, wherein the patient has not previously been treated for cancer.

63. The method of claim 52, wherein the patient has been previously treated for cancer.

64. The method of claim 52, wherein the cancer is refractory to radiation therapy.

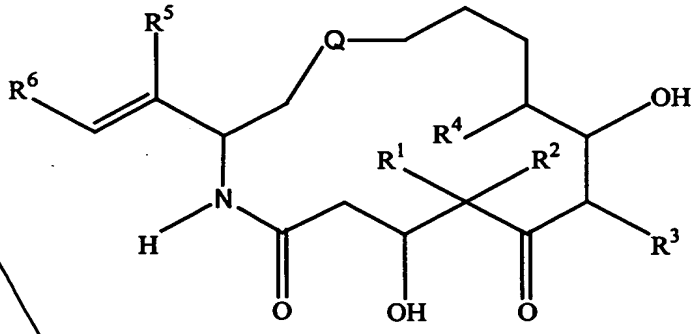
65. The method of claim 52, wherein the cancer is refractory to anti-cancer chemotherapy.

66. A method of treating cancer in a patient previously experiencing neurotoxicity comprising intravenously administering to said patient a therapeutically effective amount of the pharmaceutical formulation of claim 47 diluted in a parenteral diluent as a weekly infusion, wherein the total dose of the compound of formula I is less than about 200 mg/m^2.

67. The method of claim 52, wherein the cancer is a solid tumor.

68. The method of claim 30, wherein the cancer is a solid tumor.

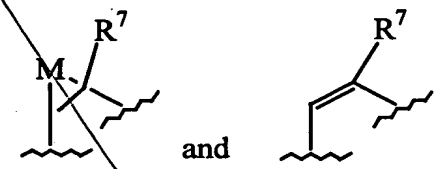
69. A method of treating cancer while reducing or avoiding neurotoxicity which comprises intravenously infusing a therapeutically effective amount of compound represented by formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO_2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof;

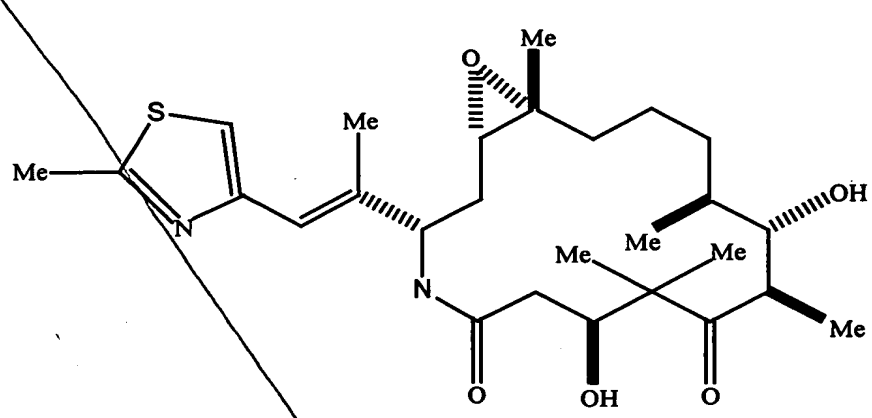
over a period of one (1) hour to a patient in need thereof.

70. The method of claim 69, wherein the infusion is made on a weekly basis.

71. The method of claim 69, wherein the therapeutically effective amount is from about 1 mg/m^2 to about 65 mg/m^2.

72. The method of claim 71, wherein the amount is 25 mg/m^2.

73. The method of claim 69, wherein the compound of formula I is



74. The method of claim 69 which further comprises orally administering said compound 1 week before or after an intravenous administration.

75. A method of treating cancer in a human patient in need thereof with a synthetic or semi-synthetic epothilone analogue that is active against cancer which comprises a four (4) week dosing cycle wherein said cycle comprises three weeks of weekly intravenous administration and one week of oral administration of said epothilone analogue.

76. The method of claim 31, wherein the compound is administered daily or weekly.

77. The method of claim 32, wherein the compound is administered daily or weekly.

78. The method of claim 76 wherein the compound is administered daily for 3 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

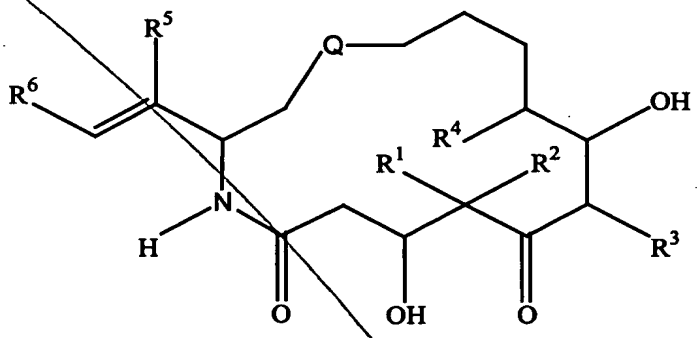
79. The method of claim 77 wherein the compound is administered daily for 3 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

80. The method of claim 76 wherein the compound is administered daily for 5 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

81. The method of claim 77 wherein the compound is administered daily for 5 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

82. The method of claim 31 wherein the compound of formula I is administered as one or more 28 day cycles, wherein the compound of formula I is administered orally on day 1 and as an IV infusion on days 7, 14 and 21.

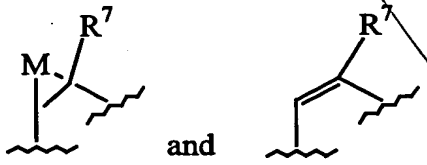
83. A method of treating cancer in a patient comprising intravenously or orally administering to said patient a therapeutically effective amount of a compound represented by formula I:



I

wherein:

Q is selected from the group consisting of



;

M is selected from the group consisting of oxygen, sulfur, NR^8, and CR^9R^{10};

each R^1, R^2, R^3, R^4, R^5, R^7, R^{11}, R^{12}, R^{13}, R^{14} and R^{15} is, independently, selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl and heterocyclo, and wherein R^1 and R^2 are alkyl, they can be joined to form a cycloalkyl;

R^6 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocyclo and substituted heterocyclo;

R^8 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, $R^{11}C=O$, $R^{12}OC=O$ and $R^{13}SO^2$; and

each R^9 and R^{10} is, independently, selected from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, aryl, heterocyclo, hydroxy, $R^{14}C=O$, and $R^{15}OC=O$;

and any salts, solvates, or hydrates thereof.

84. The method of claim 83, wherein the compound of formula I is administered orally in a dose of about 0.05 mg/kg to 200 mg/kg.

85. The method of claim 83, wherein the compound of formula I is administered intravenously at a dose of about 1 mg/m^2 to 65 mg/m^2.

86. The method of claim 84, wherein the compound is administered daily or weekly.

87. The method of claim 85, wherein the compound is administered daily or weekly.

88. The method of claim 86 wherein the compound is administered daily for 3 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

89. The method of claim 87 wherein the compound is administered daily for 3 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

90. The method of claim 86 wherein the compound is administered daily for 5 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.

91. The method of claim 87 wherein the compound is administered daily for 5 days with a period of 1 week to 3 weeks between cycles where there is no administration of the compound.